Journal of Orthopedic Research and Therapy
Hammond EA, et al. J Orthop Res Ther 7: 1266.
www.doi.org/10.29011/2575-8241.001266
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Research Article

Electro Acupuncture is not Recommended for Managing Chronic Neuropathic Pain in Chemotherapy Induced Peripheral Neuropathy: A Double Blind Randomized Controlled Trial

Elizabeth Andersen Hammond[1*], Marshall Pitz[2], Pascal Lambert[3], Barbara Shay[1]

[1]Department of Physical Therapy, College of Rehabilitation Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

[2]Medical Oncologist and Associate Professor of Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

[3]Epidemiology and Cancer Registry, Cancer Care Manitoba, Winnipeg, Canada

[*]**Corresponding author:** Elizabeth Andersen Hammond, Department of Physical Therapy, College of Rehabilitation Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba R3E 0T6, Canada

Citation: Hammond EA, Pitz M, Lambert P, Shay B (2022) Electro Acupuncture is not Recommended for Managing Chronic Neuropathic Pain in Chemotherapy Induced Peripheral Neuropathy: A Double Blind Randomized Controlled Trial. J Orthop Res Ther 7: 1266. DOI: 10.29011/2575-8241.001266

Received Date: 07 November, 2022; **Accepted Date:** 14 November, 2022; **Published Date:** 17 November, 2022

Abstract

Purpose: Research on acupuncture treatment for Chemotherapy Induced Peripheral Neuropathy (CIPN) lack important scientific standards that include homogenous populations, sham control groups, and valid and reliable outcome measures. This prospective double-blind Randomized Controlled Trial (RCT) sought to answer whether Electro Acupuncture (EA) could improve chronic neuropathic CIPN pain in breast cancer patients exposed to taxane chemotherapy compared to a sham acupuncture control group.

Methods: 18 participants were recruited from the cancer registry at CancerCare Manitoba. The primary outcome measure was the Numeric Pain Rating Scale (NPRS). Subjective questionnaires and Quantitative Sensory Testing (QST) were used to establish nerve pain and function for baseline and follow up post 6-week trial. Acupuncture treatment consisted of bilateral points LR3, LI4 and ST36 with EA at 2Hz at maximum tolerance bilaterally x 30 minutes, once a week over 6 weeks. Sham acupuncture using Streitberger Placebo Needles (Asiamed) included the same points and treatment parameters.

Results: Baseline NPRS scores were equal between the groups with sham median (Q1-Q3) 5.5 (4.75-6.0) and true 5.0 (3.5-7.75) NS. Post pain scores revealed a statistically significant and clinically relevant improvement for the sham group with a reduction in pain to 2.50 (2.0-3.0), p=0.04 compared to the true EA group 4.25 (3.25-5.0) that demonstrated no clinical or statistical improvement.

Conclusion: This trial used best practice, incorporated a homogeneous population, used valid and reliable outcome measures, and sham controls. The evidence suggests that EA does not provide superior analgesia compared to placebo acupuncture and may reduce the placebo response.

Keywords: Acupuncture, electro acupuncture; Breast cancer; Chemotherapy Induced Peripheral Neuropathy (CIPN)

Introduction

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a leading complaint among cancer survivors and can result in lasting symptoms of neuropathic pain or hypoesthesia [1]. Despite the prevalence and persistence of symptoms, there are currently few treatments available [2]. The majority of patients on chemotherapy treatment will seek Complementary Alternative Medicine (CAM) to assist with symptoms during and after cancer treatment [3,4]. CAM encompasses a variety of treatments ranging from homeopathy to mindfulness. A few of these treatments such as meditation and relaxation can be valuable, while others (such as acetyl-L-carnitine) have been shown to exacerbate CIPN symptoms [5]. Evidence of the benefit or harm of CAM treatments is difficult to determine as many of these treatments have not been scientifically tested [1,6,7]. Acupuncture is part of CAM and a popular choice for many breast cancer patients. The National Institute of Health consensus statement in 1997 and a prospective randomized controlled trial for electro acupuncture (EA) and chemotherapy-induced emesis have led to increasing acceptance among cancer patients and the medical community [8-10]. The efficacy for acupuncture specific to the treatment of cancer pain is limited. Further, the current research for acupuncture and CIPN treatment lack important scientific standards including homogenous populations, sham placebo groups, valid and reliable outcome measures, reported acupuncture points, treatment time and duration [8,11-14]. This study sought to answer clearly whether a combination of acupuncture and EA (used to strengthen the clinical response) could improve neuropathic pain CIPN symptoms in breast cancer patients exposed to taxane chemotherapy compared to a sham placebo control group.

Methods

Participants and Eligibility

Patients were recruited from the cancer registry at CancerCare Manitoba. All stage I-III, first cancer patients with primary breast cancer diagnosed in 2015 and 2016 that received docetaxel chemotherapy were contacted via letter. The letter indicated that an acupuncture trial was recruiting for the treatment of painful CIPN symptoms and contained contact information for the research coordinator. Participants were screened over the phone with the Self report of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire and a Numeric Rating Pain Scale (NPRS). A score >12 on the S-LANSS and an NPRS 3/10 or higher were eligible for participation. Exclusion criteria were co-morbid conditions that cause peripheral neuropathic symptoms, medical co-morbidities that are contraindications for acupuncture, lymphedema, pain not specific to fingers/toes, and pain not neuropathic in origin (SLANSS <12 and NPRS <3/10).

Protocol

Ethics approval was obtained from the Health Research Ethics Board (HREB) at the University of Manitoba (H2015:282) and the Research Resource Impact Committee at CancerCare Manitoba (2015:042). Clinical trials number NCT02821442. After consent, an initial assessment for baseline nerve function testing was completed. Self-reported data and Quantitative Sensory Testing (QST) were used to establish nerve pain and function for baseline and the follow up post 6-week trial. Quantitative Sensory Testing (QST) is a valid, reliable and reproducible measure frequently used in research for diagnosing and assessing small fibre neuropathies such as CIPN [15,16]. QST accurately measures somatosensory characteristics at specific time points and provides information on larger myelinated (Aβ), small thinly myelinated (Aδ), and unmyelinated (C-fibre) function or dysfunction. The most painful of either the fingers or toes was chosen for testing. Follow up assessment (blinded assessor) occurred 2-4 days after the six-week trial to repeat the nerve assessment and self-report questions. After the final assessment, those allocated to sham acupuncture were offered true acupuncture. However, since preliminary data analysis revealed statistically and clinically significant change in pain scores for the sham placebo group, and no change except possibly maintaining neuropathic pain, the study was terminated.

Outcome Measures

Primary

1) Numeric Rating Pain Scale (NPRS) - was the primary outcome measure. A verbal description (0-10) on the intensity of CIPN pain on each visit was assessed. 0 indicated 'no pain' while 10 indicated 'worst pain imaginable'. A minimum of 3/10 was required for study enrolment.

2) Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) - is a valid, sensitive and specific questionnaire and was used to confirm the resolution of neuropathic pain and symptoms [17]. A score equal to or >12 was required for study enrolment to confirm presence of neuropathic symptoms, ensuring a relatively homogenous sample.

Secondary

3) Quantitative Sensory Testing

i. Thermal cold pain thresholds (Neurosensory Analyzer TSAII, Medoc, Israel) - measured Aδ and C-fibre function. Increased sensitivity to thermal pain thresholds results in thermal hyperalgesia and has been described as a common feature of both neuropathic pain and painful CIPN. The TSA II thermode was attached to the tip of the palmar surface of the distal phalanx of the index finger or plantar surface of the big toe. Temperature was decreased by 0.1-degree Celsius (˚C) increments until the participant pressed a button indicating thermal pain. The test immediately stops when the participant presses the button and the temperature returns to baseline (32 ˚C). The participant is always in control and is never at risk for tissue damage (temperature limits are set to vary only from 0-50 ˚C. Thermal hyperalgesia is defined as a painful response at >18 ˚C.

ii. Pressure/pain thresholds (pain pressure algometer) - was selected as a measure of central sensitization. A hand-held device (Somedic AB, Sweden) was applied perpendicular to the left quadriceps muscle. The quadriceps muscle is distant from the source of pain and a lower tolerance to pressure suggests the possibility of central sensitization. Increasing pressure is applied until the participant determines that the sensation has changed from a feeling of pressure to a feeling of pain. The test stops when the participant presses the button indicating pain, and force (Kpa) is recorded.

4) Participants' expectations for potential recovery with acupuncture treatment were recorded on initial assessment. Expectation is known to play a large role in treatment response and helped to confirm between group similarities.

5) Belief - a post treatment question whether the participant believed they were in the true versus sham acupuncture condition that was recorded on the final assessment.

The protocol was based on consensus recommendations for optimal treatment, sham controls and blinding from the International Acupuncture Research Forum, and the standards for reporting interventions in clinical trials of acupuncture (STRICTA) [18-22]. Both the outcome assessor and participants were blinded to the intervention groups. Random numbers were assigned to each group and envelopes containing treatment or sham were pre-randomized, sealed, and provided to the experienced acupuncturist prior to trial enrolment by a member of the research team not connected to recruitment or assessment. True acupuncture consisted of acupuncture points ST36, LR3, and LI4 bilaterally x 30 minutes, once a week for 6 weeks. EA was applied to ST36 where electrical current was transmitted through the needles at 2Hz and the maximum tolerated intensity (ES-130 Portable Japanese Electro-Acupuncture Device, UPC Medical Supplies Inc. South El Monte, CA, USA). These points were selected using points and treatment times previously shown to be effective [20,22-27]. Sham placebo acupuncture using Streitberger Placebo Needles (Asiamed) included the same points and treatment parameters, but the placebo needles do not penetrate the skin and the current for EA was not turned on. Streitberger placebo needles are virtually indistinguishable from true acupuncture needles [28]. The end of the needle is blunted so that it cannot penetrate the skin. The handle telescopes similar to magicians' 'fake dagger', and the illusion results in the participant thinking they received true acupuncture. Multiple sensory systems are misled as the participant feels the sharp 'pin-prick' sensation, sees the needle penetrating and the blinking green light from the electrical stimulus device, convincing the individual that real treatment has been provided. Participants had painful CIPN symptoms in either the hands, the feet or both. The most painful of either the hands or feet was tested at the Pain Research Laboratory, University of Manitoba. As acupuncture is a systemic treatment, it was appropriate to select the most painful site for study and our outcomes were sensitive and specific to either the hands or the feet.

Data Analysis

NPRS values pre- and post-intervention between the treatment and control groups were compared using the Mann-Whitney test. S-LANSS values post-intervention were compared using the Fisher's exact test. Delta scores from pre-intervention to post-intervention assessments were calculated for cold pain scores and pain pressure scores. Independent t-tests were used to compare cold pain scores, whereas the Mann-Whitney test was used for pain pressure because the assumption of normality was not met. All analyses were run using the R project for statistical computing software version 3.4.1. (R. Development team, 2017).

Results

Our initial cancer registry letter resulted in 40 phone calls indicating interest in participation. Of these, 19 female participants met the inclusion criteria and were invited to participate. Ineligibility of the interested participants was due primarily to other pain not defined as neuropathic in origin (S-LANSS<12). One participant withdrew from the study after the first acupuncture treatment session as she believed her pain increased significantly with acupuncture. Interestingly, she had been randomized to the sham group and had only received placebo needles. To meet the minimum criteria of CIPN pain for 6 months, participants had to have completed their chemotherapy at least 2 years prior to the study. Sixteen of 18 participants completed chemotherapy 3 years before, with the remaining 2 participants completing treatment the following year. Ten participants in the true treatment and 8 in the sham completed the trial. Pain was primarily reported as being the worst in the feet (n=13) versus the hands (n=5). The primary outcome measure was the change in pain score. A change score of 2 for the NPRS is defined as clinically relevant [29]. Baseline NPRS scores were equal between the groups with sham median (Q1-Q3) 5.5 (4.75-6.0) and true 5.0 (3.5-7.75) NS. Post pain scores revealed a statistically significant and clinically relevant improvement for the sham group with a reduction in pain to 2.50 (2.0-3.0), p=0.04, compared to the true acupuncture group 4.25 (3.25-5.0) that demonstrated no clinical improvement. Figure 1. shows the median and IQR of true versus sham pain scores pre and post treatment. SLANSS scores also changed post-treatment. While everyone had to have a score >12 before the trial to define the pain as neuropathic, only one person continued to score >12 after sham treatment, indicating that 7/8 sham treatment individuals perceived their pain as being different (less neuropathic symptoms of burning, shooting, hypersensitivity). The true acupuncture group were more likely to maintain the description of pain being neuropathic in origin with 6/10 scoring >12. Comparison of the post treatment S-LANSS scores between the sham and true groups were not significant; however, the difference approached statistical significance (p=0.06). Thus, the data was trending that true EA had less effect on neuropathic pain descriptions compared with sham acupuncture.

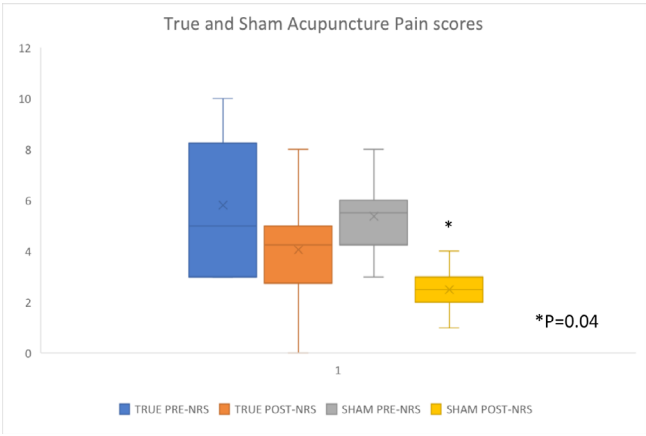

Figure 1: Pre and post treatment pain scores. The box and whisker plots indicate the pain scores for participants randomized to either true (n=10) or sham (n=8) acupuncture. The line represents the median score. The boxes indicate the 25th and 75th percentile and the whiskers are the highest and lowest values. The values along the y axis are NPRS scores from 0-10 where 0=no pain and 10= the worst pain imaginable.

Since expectation can influence the outcome in studies involving placebo participants' expectations for recovery with acupuncture were noted. At initial assessment, all 18 participants either believed acupuncture would help their symptoms (n=3 in treatment and n=1 in sham) or had heard it could help and were wanting to 'give it a try' (n=7 in treatment and n=7 in sham). Post treatment, when asked if acupuncture treatment helped their pain, 13 of 18 (72.2%) believed they were better. Of the 5 participants that felt their pain was not helped, 3 were in the treatment group and 2 were in the sham. Therefore, 70% of participants in the true (n= 7) and 75% of sham group (n= 6) believed acupuncture had improved their pain. Individual change scores of the participants in the true and sham groups are plotted in Figure 2A and 2B. None of the participants were worse with the majority having decreased pain scores post-treatment compared to baseline. To verify that the sham group received a believable placebo, participants were asked at the end of the study in which group they thought they had been randomized. One participant in the true acupuncture group believed they had received sham treatment, while two in the sham group were unsure of sham versus true acupuncture allocation. With respect to the results in Quantitative Sensory Testing (QST), there was no difference in QST measures for changes in cold pain (p=0.64) thresholds and there was no difference in pressure pain thresholds (p=0.18).

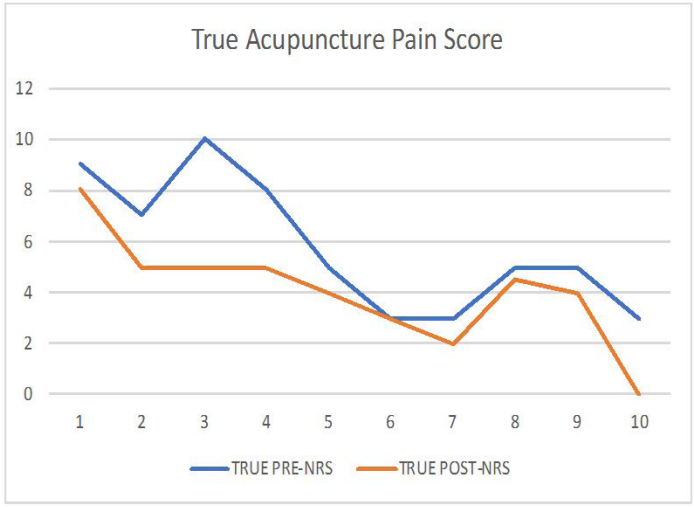

Figure 2A: Pre and post treatment pain scores. The line graph indicates the pain scores for participants randomized to true (n=10) acupuncture. The blue line represents the median pre-treatment NPRS score. The orange line represents post-treatment NPRS scores. Participants are along the x-axis and NPRS scores are along the y axis. The NPRS ranks pain from 0-10 where 0=no pain and 10= the worst pain imaginable.

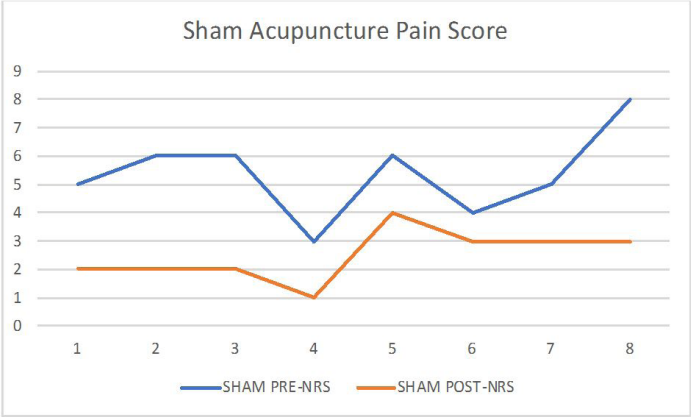

Figure 2B: Pre and post sham pain scores. The line graph indicates the pain scores for participants randomized to sham (n=8) acupuncture. The blue line represents the median pre-sham NPRS score. The orange line represents post- NPRS scores. Participants are along the x axis and NPRS scores are along the y axis. The NPRS ranks pain from 0-10 where 0=no pain and 10= the worst pain imaginable.

Discussion

The results of this trial were surprising. In an effort to maximize the treatment effect due to the true intervention, the parameters chosen included 2 Hz EA applied at ST36 at the strongest tolerable intensity. At this intensity, there were no benefits of EA for the treatment of chronic neuropathic CIPN pain. In fact, preliminary analysis confirmed that true electro acupuncture treatment was not resulting in improved pain scores or the expected placebo response. At minimum, it was expected that pain scores would be equal to sham acupuncture (pain reduction by 45%), even if true EA was ineffective. We had concerns that EA potentially may be maintaining the neuropathic pain. Interestingly, despite no statistically significant or clinically relevant change in pain for the treatment group, 70% of the participants subjectively reported that EA treatment had helped their symptoms. The participants' recollection of the effectiveness of acupuncture contrasted with the QST and subjective questionnaire data. This highlights the importance of using valid and reliable outcome measures to monitor change over time. Individual reflection on experience and memory is clearly not objective. It may seem improbable in a chronic pain state that the sham group improved by 45%. Likely, the pain reduction reported post sham placebo treatment would not have persisted, and participants pain would have returned shortly after re-assessment. The placebo literature supports the dramatic improvements in the sham group and explains how this would be expected. Placebo research describes the power of expectation and hope in modulating neuro immune responses and the pain processing network. Central nervous system pain modulation affects the descending noxious inhibitory control system, the anterior cingulate cortex, amygdala, dorsal lateral prefrontal cortex, and the periaqueductal grey that is linked to the release of endogenous opioids and non-opioid neurotransmitters involved in analgesia. Depending on the clinical trial, placebo can account for 10-60% of the response. Specific to chronic pain states the literature varies between 26-45% [30,31]. Expectations and beliefs have a known role in stimulating the same opioid pathways as acupuncture [32]. Documenting this expectation in clinical trials can help explain the observed placebo response.

Animal models using acupuncture to produce anti-hyperalgesia help to interpret the possible physiological mechanisms and pathways that result in pain reduction. Specifically, (EA) is effective in diminishing cold hyperalgesia in rat models of chemotherapy-induced pain [33]. Moon and colleagues showed that the opioid pathway was responsible by using the opioid receptor antagonist (naloxone) which negated the effects of EA in this pain model. EA effectively diminished hyperalgesia/allodynia in rats induced with paclitaxel neuropathy, and μ, δ, and k opioid receptors were responsible for the anti-hyperalgesic response [34]. Additional rat models of neuropathic pain have confirmed that mechanical allodynia is relieved by 2-10 Hz EA and confirmed with antagonists that spinal μ and δ receptors mediate this anti-nociceptive effect [35-37]. EA has also been shown to inhibit inflammatory mediators in the spinal cord after spinal nerve ligation [38]. EA has been shown to stimulate the production of Nerve Growth Factor (NGF), Brain Derived Neurotrophic Factor (BDNF), and neurotrophin-3 (NT-3) in rats and rabbits [39-41]. These neurotrophic factors are important in stimulating the growth cone and promoting neuro regeneration after injury. While there is encouragement for the use of acupuncture/EA in animal models of pain, there is limited evidence from human clinical trials. Many systematic reviews have evaluated whether cancer specific pain can be treated with acupuncture [11,12,14,42,43]. Unfortunately, reviews recognize that the majority of studies are of low methodological quality, lack proper blinding, have high risk of bias, and have no control groups. One article, in particular, is consistently identified in many reviews to be of high methodological quality, low risk of bias, with proper randomization [44]. Alimi and colleagues published a blinded, prospective, Randomized Controlled Trial (RCT) in the Journal of Clinical Oncology, and found that auricular acupuncture was effective in treating chronic central and peripheral neuropathic pain (measured by the VAS pain scale and average electrical potential difference). This study had a heterogeneous sample population (included head and neck, breast, lung and other cancers), included all stages of cancer (including metastatic disease), treated any painful site in the body (average of 6 different painful sites per person), lacked validated outcome measures (the effect relating to pain by measuring the electrical potential difference of the ear with an electrical voltmeter has not been validated), used no outcome measures to distinguish the type of pain treated (i.e. neuropathic, nociceptive, inflammatory), and weak inclusion criteria (pain only had to be stable for one month). Their primary outcome measure was average pain at day 60 after 2 acupuncture treatments one month apart. The methodological structure of the study raises the possibility that improvements in pain scores could easily occur with passing time.

Another CIPN pilot study used Nerve Conduction Studies (NCS) as the primary outcome measure on the effectiveness of acupuncture [45]. The results demonstrated that acupuncture improved Aα fibres' velocity and amplitude signals, and that these improvements persisted 3 months post acupuncture treatment. Of significance here is that CIPN is a small fibre neuropathy affecting some Aβ, but mostly small thinly myelinated Aδ and unmyelinated C fibres, and nerve conduction studies are neither specific nor sensitive for evaluation of small fibre function. Our study used Quantitative sensory testing (QST) to provide quantitative nerve sensation data in addition to subjective reports of pain. QST is a quantitative, reliable and reproducible measure for diagnosing small fibre neuropathies (Aδ and C fibres) when adherence to protocol and attentiveness of the participant is maintained. QST can also quantify larger Aβ fibre function. CIPN symptoms begin as a small fibre neuropathy, and even small subclinical changes can be quantified with repeated measures of QST [46-49]. Our study found no improvement to thermal pain or pressure pain thresholds with EA. Low frequency (2-4 Hz) and high frequency (100 Hz) EA are established frequencies used in research and clinical practice and known to stimulate different pain modulation pathways [50-52]. The optimal frequency is thought to activate endogenous

opioid and descending noxious inhibitory control (DNIC) by stimulating Aδ fibres that, in turn, release endorphins and serotonin in the brain [18,53,54]. In agreement with our results, another study found EA treatment was equal to placebo for participants with CIPN [49]. Unfortunately, the methods chosen (specifically the treatment schedule, EA dosage time and frequency at 50 Hz) are not comparable to other animal/human studies [50-52]. The subjective CIPN complaints of the participants also differed substantially with some having pain, numbness, paresthesia, or functional impairments in the hands or feet. In addition, the inclusion criteria in the Rostock study allowed for multiple cancers, multiple chemotherapy regimens, and treatment at different time points post chemotherapy; that is, substantial heterogeneity, thus making it difficult to determine efficacy.

The Clinical Oncology Society of Australia published a position statement on Complementary Alternative Medicine (CAM) identifying the growing acceptance among patients and the urgent need for clinicians to support research to clarify the potential benefit or harm, and define the role in cancer care [55]. With patients seeking CAM, evidence for use in cancer symptom management is required to assess the benefits and risks. In terms of this current study, strict inclusion criteria ensured homogeneity, clearly defined methods allowed for repeatability, and acupuncture treatments selected from previous studies shown to be effective were employed. Both the participant and assessor were blinded to the treatment, and sham placebo controls were used. Clearly a recognized limitation is the small sample, size which offers the possibility that the observed differences may be due to random effect. Importantly, these factors do not explain our results that true EA at these stimulation and treatment parameters imparts no analgesic effect and may possibly maintain neuropathic pain. Future acupuncture studies should use acupuncture alone to make further conclusions.

Conclusion

This prospective double-blind RCT used best practice and STRICTA guidelines for EA incorporating a homogeneous population, valid and reliable outcome measures, and sham controls. We believe that this current study demonstrates that patients should not seek EA treatment for neuropathic pain due to CIPN.

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